REMARKS

Upon entry of this amendment, claims 1-13 and 16 are pending. An amendment to claim 1 is proposed herein. The amendment add no new matter.

Rejection under 35 U.S.C. §102(b):

Claims 1-6, 12-13 and 16 are rejected under 35 U.S.C. §102(b) as lacking novelty over WO 97/09342, Arenas et al. The Office Action states that the Arenas et al. reference teaches a high throughput assay for identifying a test compound that binds to a target RNA comprising (a) contacting said test compound to said target RNA in the presence of conformation-specific nucleases (RNA modifying enzymes)," and "(b) measuring or detecting the modification of said target and comparing the amount of modification relative to a control or standard and identifying whether said test compound binds to said target. Applicants respectfully disagree.

Applicants submit that claim 1 as amended requires that the RNA-modifying enzyme "covalently alters an existing base in said target RNA." Support for the amendment is found in the specification at page 8, lines 15-17, which state "The modification typically involves the covalent addition to, or alteration of, existing bases in RNA." The specification provides numerous examples of base alterations in Figure 1, Table 1 (page 12), and in the specification at, for example, page 8, line 19 to page 10, line 29. One skilled in the art would readily recognize a covalent alteration of a base comprised by an RNA target. One skilled in the art would also know whether a given RNA modifying enzyme covalently alters a base comprised by the RNA target.

The Office Action acknowledges that the Arenas et al. reference does not teach a methylase as the RNA-modifying enzyme. Similarly, Applicants submit that the Arenas et al. reference does not teach an RNA modifying enzyme that covalently alters an existing base in the target RNA. The reference states:

> "In either case, determination of the absolute amounts of folded and unfolded target RNA, the folded:unfolded ratio, or the rates of folding or unfolding, may be carried out using any method, including without limitation hybridization with complementary nucleotides, treatment with

> conformation-specific nucleases, binding to matrices specific for single-stranded or double-stranded nucleic acids, and fluorescence energy transfer between adjacent fluorescence probes." (Arenas et al., p. 12, lines 7-10)

Applicants submit that a conformation-specific nuclease, which cleaves a phosphodiester bond between nucleotides, does not "covalently alter an existing base in the target RNA." The reference does not teach contacting a test compound with target RNA and an RNA modifying enzyme that alters an existing base in the target RNA as required by the claim as amended. As such, Applicants submit that claim 1 and claims 2-6, 12 and 13 are novel over the Arenas et al. reference.

With regard to claim 16, Applicants submit that Arenas et al. does not disclose the use of a target RNA that comprises a suicide substrate for the enzyme, or detecting the modification of the enzyme by the suicide substrate. Arenas et al. teaches that "the addition of non-specific DNA or RNA may also be necessary to minimize the effect of nucleic acid-reactive molecules (such as, for example, intercalating agents) that would otherwise score as 'hits' in the assay" (page 11, lines 24-26). Applicants submit that non-specific DNA or RNA is not a suicide substrate as recited in claim 16. The instant specification describes the use of, and defines "suicide substrate" as follows:

> As an alternative to detecting or measuring RNA modification in step (b), the methods of the invention can involve the detection or measurement of the modification of the RNA-modifying enzyme by the incorporation of a non-competitive, irreversible, suicide substrate *from the target RNA*. As used herein, the term "suicide substrate" refers to an enzyme substrate, e.g., *a **target** RNA or a nucleotide or base within the **target** RNA, that when modified by the enzyme, irreversibly binds to and inhibits the further activity of the enzyme*. Under these circumstances, one detects the activity of the enzyme on the target RNA by detecting a label incorporated into the target RNA that becomes bound to the enzyme. (page 13, line 26 to page 14, line 3; emphasis added)

In view of this definition, Applicants submit that the inclusion of a non-specific DNA or RNA as taught by Arenas et al. does not satisfy the requirements for a "suicide substrate" as recited by claim 16. Not only does a non-specific DNA or RNA as taught by Arenas et al. not irreversibly bind to the enzyme and inhibit its further activity, but the definition recited above and the claim itself both make it clear that the *target* RNA

comprises the suicide substrate. Because a non-specific DNA or RNA is not a *target* RNA, the addition of such a non-specific competitor cannot satisfy the requirements for a suicide substrate. Because Arenas et al. does not teach a suicide substrate as recited in claim 16, the reference cannot anticipate that claim.

In view of the above, Applicants submit that claim 1 as proposed to be amended herein, claims dependent from it, and claim 16 are novel over Arenas et al. Applicants respectfully request withdrawal of the §102 rejections over this reference.

Rejection under 35 U.S.C. §103:

Claims 7-11 are rejected under 35 U.S.C. §103(a) as obvious over Arenas et al. in view of Cundliffe et al., 1979, Nature 278: 859-861. The Office Action states that the Arenas et al. reference does not teach "a RNA modifying enzyme as methylases." The Office Action then states that Cundliffe et al. teaches "a method for ribose methylation and resistance to a test compound, thiostrepton, wherein Cundliffe et al. disclose that RNA-ribose methylase incorporates a single methyl-group in thiostrepton-resistant ribosomes." The Office Action continues, stating "Cundliffe et al. also teach that (i) RNA-modifying enzyme as RNA ribose methylase (ii) incorporation could be detected by the incorporation of an isotopic label from S-adenosyl-methionine into the target RNA; presence of nucleotides (purine or pyrimidine bases) inhibited or not adsorbed the incorporation of methyl groups into the target RNA and binding of thiostrepton to the target and erythromycin induced methylase." (citations to specific pages and paragraphs omitted).

The Office Action concludes that it would have been obvious to one of skill in the art at the time of the invention to combine a method of screening for a test compound that binds to a target RNA as taught by Arenas et al. with the methylases (RNA modifying enzyme) taught by Cundliffe et al. to achieve the expected advantage of developing a sensitive and high-throughput method for screening test compounds that specifically bind to target RNA. Applicants respectfully disagree.

Applicants submit that there is no motivation to combine the references in the way suggested by the Office Action because neither reference teaches or suggests the use of a methylase to measure the conformation of a target RNA. The Arenas et al. method teaches the use of a conformation-specific nuclease to detect changes in the *conformation* of the target RNA caused by binding of a test compound. Applicants submit that the Arenas et al. method strictly relies on the determination of effects of a test compound on the conformation, and more specifically the folding, of the target RNA. The Examiner's attention is drawn to page 11, line 27 to page 12, line 17 of the Arenas et al. reference, which describes the methods contemplated by Arenas et al. for measurement of binding of a test ligand. The Arenas et al. reference states:

> "Binding of a test ligand to the target RNA is assessed by comparing the absolute amount of folded or unfolded target RNA in the absence and presence of test ligand, or, alternatively, by determining the ratio of folded:unfolded target RNA or change in the folded state of the target RNA, or the rate of target RNA folding or unfolding in the absence and presence of test ligand." (page 11, lines 27-31; emphasis added)

Arenas et al. also states:

> In either case, *determination of the absolute amounts of folded and unfolded target RNA, the folded:unfolded ratio, or the rates of folding or unfolding*, may be carried out using any method, including without limitation hybridization with complementary oligonucleotides, treatment with *conformation-specific* nucleases, binding to matrices specific for single-stranded or double-stranded nucleic acids and fluorescence energy transfer between adjacent fluorescence probes. (page 12, lines 7-12; emphasis added)

Finally, claim 1 of the Arenas et al. patent application specifically requires, in step (d), "*measuring the conformation* of the target RNA sequence in each combination."

In view of the above, Applicants submit that the teachings of Arenas et al. strictly require the detection of conformation or conformational change induced by the binding of an RNA binding compound. Thus, the suggested use of a conformation-specific nuclease by Arenas et al. absolutely requires the conformation-specific aspect of that nuclease. Applicants submit that neither Arenas et al. nor Cundliffe et al. teaches or suggests the use of a methylase for the detection of conformation or conformational change. The

Office Action acknowledges that Arenas et al. is silent on methylases. Cundliffe et al. teaches that methylation of rRNA is a mechanism of resistance to thiostrepton, i.e., methylated rRNA does not bind the thiostrepton antibiotic. There is no teaching in the Cundliffe et al. reference that the methylase is useful to measure the conformation of the rRNA. Because the Arenas et al. reference absolutely requires the measurement of conformation in its method, and because neither Arenas et al. nor Cundliffe et al. teaches or suggests the use of a methylase for the measurement of conformation, Applicants submit that one of skill in the art would not have been motivated to combine the references in the manner suggested by the Office Action. Because there is no motivation to combine the references in the manner suggested by the Office Action, Applicants submit that the claimed invention cannot be obvious over that combination. Applicants respectfully request the withdrawal of the §103 rejection of claims 7-11 over these references.

In view of the above, Applicants submit that all issues raised in the Final Office Action have been addressed herein. Applicants respectfully request reconsideration of the claims.

Respectfully submitted,

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Version of proposed amendment marked to show changes:

1. (Amended) A method for determining whether a test compound binds to a target RNA, the method comprising the steps of:

(a) contacting said test compound with said target RNA and an RNA-modifying enzyme that covalently alters an existing base in said target RNA; and

(b) detecting the modification of said target RNA by said enzyme and comparing the amount of modification detected to that of a standard, wherein said comparing determines whether said test compound binds to said target RNA.